

# Discrete dynamic modeling of biological systems

- The functional form of regulatory relationships and kinetic parameters are often unknown
- Increasing evidence for
  - robustness to changes in kinetic parameters.
  - bistability (two steady states)

Hypothesis: the kinetic details of individual interactions are less important than the organization of the regulatory network

Discrete dynamic models assume that nodes can be characterized by only a few (minimum two) discrete states.

Discrete models can handle larger networks than continuous models.

# Boolean modeling of biological systems

Main assumption: components have two main states :

Expressed or not expressed, active or inactive, open or closed (ion channel), high or low level. Denote these states by ON (1) or OFF (0)

The changes in state are given by discrete (logical) rules.

1. Boole logic: based on the operators NOT, AND, OR

Can be defined based on set intersection and union, or input-output relations (gates, truth tables)

2. Threshold rule: the output is given by comparing the weighted sum of inputs to a threshold

# Examples of Boolean functions

<i>In</i>	<i>Out</i>
0	1
1	0

$Out = NOT\ In$

<i>In1</i>	<i>In2</i>	<i>Out</i>
0	0	0
0	1	0
1	0	0
1	1	1

$Out = In1\ AND\ In2$

<i>In1</i>	<i>In2</i>	<i>Out</i>
0	0	0
0	1	1
1	0	1
1	1	1

$Out = In1\ OR\ In2$

$$Out = \begin{cases} 1, & \text{if } -In \geq 0 \\ 0, & \text{if } -In < 0 \end{cases}$$

$$Out = \begin{cases} 1, & \text{if } In1 + In2 \geq 2 \\ 0, & \text{if } In1 + In2 < 2 \end{cases}$$

$$Out = \begin{cases} 1, & \text{if } In1 + In2 \geq 1 \\ 0, & \text{if } In1 + In2 < 1 \end{cases}$$

In	Out
0	1
1	0

Out= NOT In

In1	In2	Out
0	0	0
0	1	0
1	0	0
1	1	1

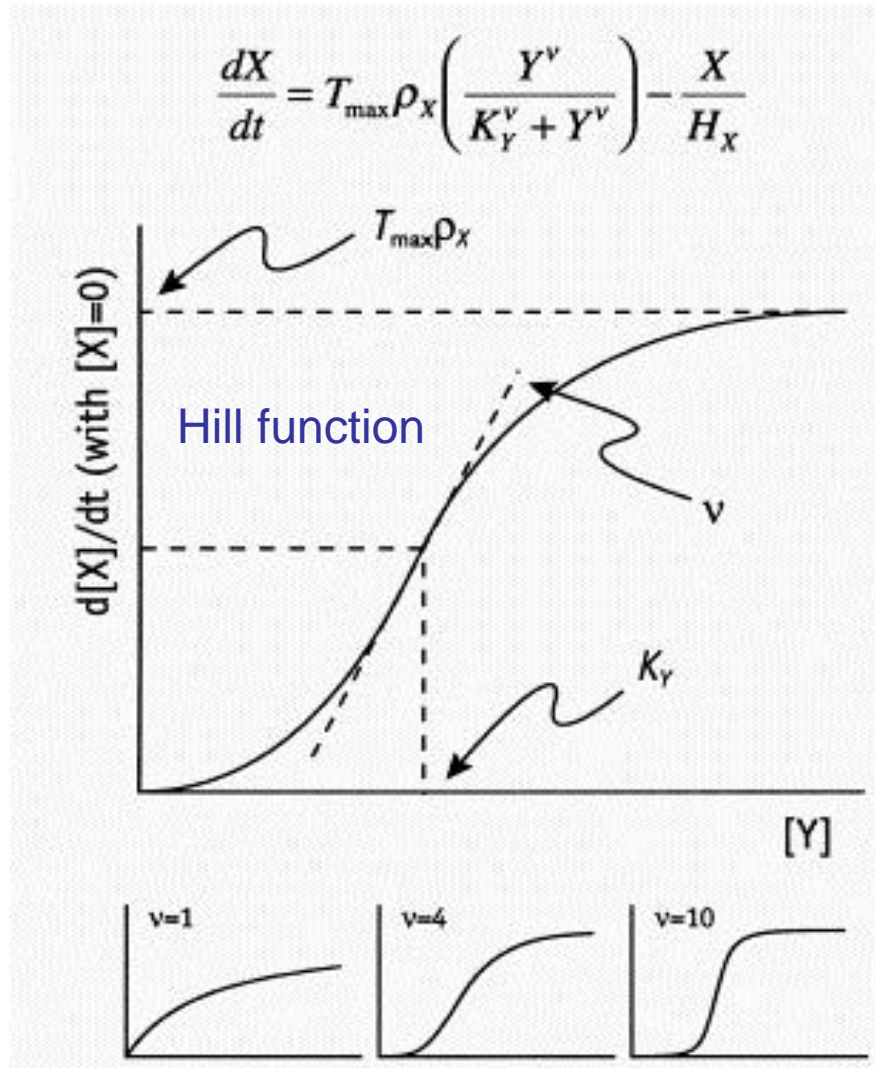
Out= In1 AND In2

In1	In2	Out
0	0	0
0	1	1
1	0	1
1	1	1

Out= In1 OR In2

Ex. Give examples for the realization of these Boolean rules in a gene regulatory network.

# From dose-response curves to Boolean switches: first step



- $X$  – mRNA
- $Y$  – transcriptional activator

If  $v$  is large, the synthesis function approaches

$$T_{\max} \rho_X B(Y)$$

$B(Y) = 1$  if  $Y \geq K_Y$  and 0 otherwise

If  $Y \geq K_Y$   $dX/dt \approx T_{\max} \rho_X - X/H_X$

If  $Y < K_Y$   $dX/dt \approx -X/H_X$

If activation is below threshold, mRNA will decay.

Q. Sketch the timecourses corresponding to the two regimes.

# Hybrid models: Boolean regulation combined with continuous decay

- Each node is characterized by both a continuous variable (concentration) and a Boolean variable (activity).

$$\frac{d\hat{X}_i}{dt} = B_i(X_1, X_2, \dots) - \hat{X}_i$$

- $X_i$  is defined by the threshold rule

$$X_i = \begin{cases} 0, & \text{if } \hat{X}_i < 0.5 \\ 1, & \text{if } \hat{X}_i \geq 0.5 \end{cases}$$

- Compared to  $\frac{dX}{dt} = T_{\max} \rho_X \left( \frac{Y^v}{K_Y^v + Y^v} \right) - \frac{X}{H_X}$ , this assumes

activation threshold=0.5, maximal synthesis rate = decay rate= 1

L. Glass, S. Kauffman, J. Theor. Biol. 39:103 1973

# Hybrid model of a positive feedback loop

$$\frac{d\hat{A}}{dt} = C - \hat{A} \quad \frac{d\hat{B}}{dt} = A - \hat{B} \quad \frac{d\hat{C}}{dt} = B - \hat{C} \quad A, B, C = \begin{cases} 0, & \text{if } \hat{A}, \hat{B}, \hat{C} < 0.5 \\ 1, & \text{if } \hat{A}, \hat{B}, \hat{C} \geq 0.5 \end{cases}$$

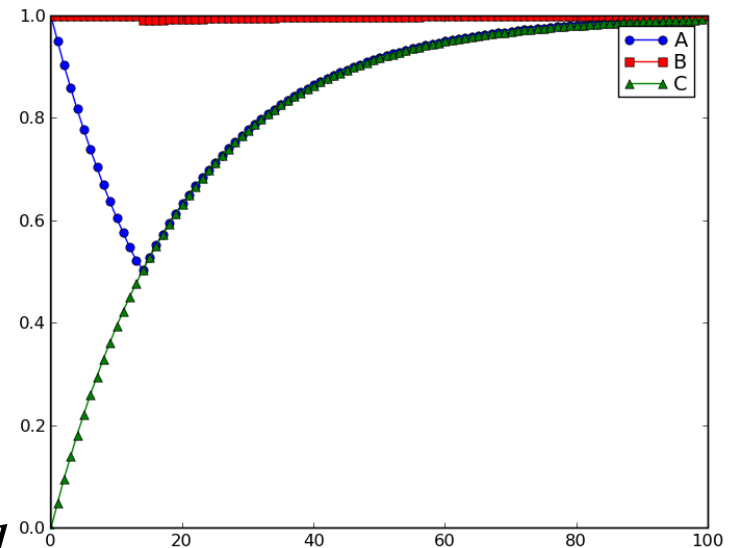
Initial condition:  $A = B = \hat{A} = \hat{B} = 1 \quad C = \hat{C} = 0$

$$\begin{aligned} \frac{d\hat{A}}{dt} &= -\hat{A} & \hat{A} &= e^{-t} \\ \frac{d\hat{B}}{dt} &= 1 - \hat{B} & \hat{B} &= 1 \\ \frac{d\hat{C}}{dt} &= 1 - \hat{C} & \hat{C} &= 1 - e^{-t} \end{aligned}$$

until  $t_1 = \ln 2$  when  $C=1$

$$\begin{aligned} \frac{d\hat{A}}{dt} &= 1 - \hat{A} & \hat{A} &= 1 - e^{t_1 - t} \\ \frac{d\hat{C}}{dt} &= 1 - \hat{C} & \hat{C} &= 1 - e^{-t} \end{aligned}$$

Steady state:  $A = B = C = \hat{A} = \hat{B} = \hat{C} = 1$

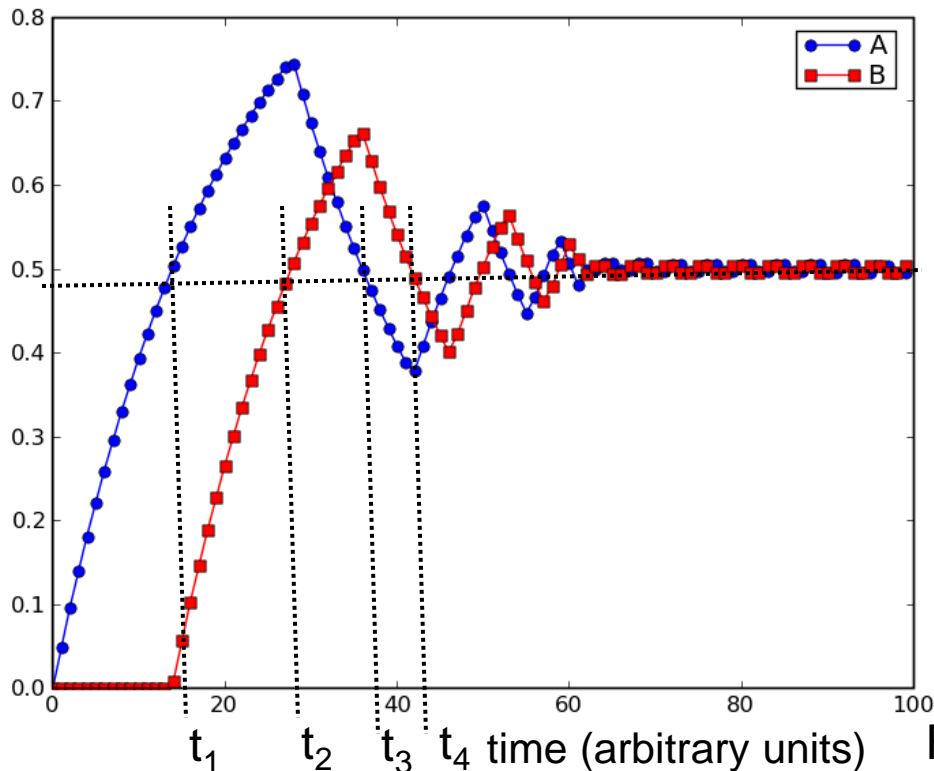


# Hybrid model of a negative feedback loop

$$\frac{d\hat{A}}{dt} = \text{not } B - \hat{A} \quad \frac{d\hat{B}}{dt} = A - \hat{B}$$

$$A, B = \begin{cases} 0, & \text{if } \hat{A}, \hat{B} < 0.5 \\ 1, & \text{if } \hat{A}, \hat{B} \geq 0.5 \end{cases}$$

Initial condition:  $A = B = \hat{A} = \hat{B} = 0$



$0 \leq t < t_1$ :  $A=B=0$

$t_1 \leq t < t_2$ :  $A=1, B=0$

$t_2 \leq t < t_3$ :  $A=B=1$

$t_3 \leq t < t_4$ :  $A=0, B=1$

$t_4 \leq t < t_5$ :  $A=B=0$

.....

Discrete state transitions at discrete time points.

It may be sufficient to characterize the state transitions without explicitly considering time.

Figure generated with BooleanNet  
<http://code.google.com/p/booleannet/>



# From dose-response curves to Boolean switches: second step

- X – mRNA
- Y – transcriptional activator

Boolean simplification:

X and Y can only have two states: ON (above threshold) and OFF (below threshold)

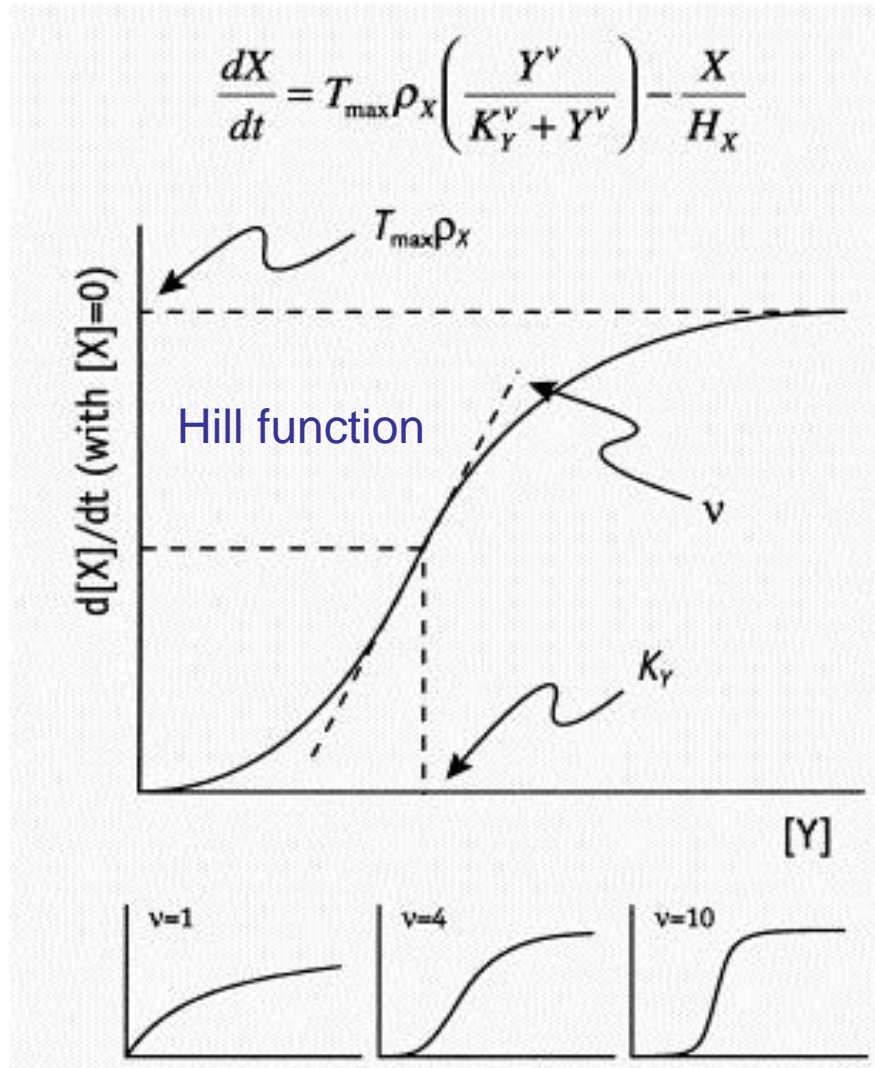
$$X^* = Y$$

Activation:

If Y=ON  $X^*=$ ON

Decay:

If Y= OFF  $X^*=$ OFF



# Implementing time in discrete models

## 1. Synchronous models

- The state of each node is updated simultaneously at multiples of a common timestep.
- Thus the future state means the state at the next timestep
- Underlying assumption: the timescales of all synthesis and decay processes are similar

## 2. Asynchronous models

The state of each node is updated individually

Implementations:

- Different update time for each node  $T_i^k = k\gamma_i$
- Select a random update order in each timestep
- Update a randomly selected node in each timestep

Ex.3

Consider a three-node network (actually, no need to construct the network). Implement the three asynchronous update methods to give a sequence of 15 node updates.

Which update method is deterministic and which is stochastic?

Ex. 4

Formulate the Boolean correspondent of the negative feedback loop hybrid model example.

What type of update will give the same state sequence as the hybrid model?

# Boolean models of regulatory networks

- Start with a known or reconstructed network.
- The directed edges in the network indicate regulator – target pairs.
- Assume that the state of each node can be 0 or 1.
- The rule giving the new state of each node is determined by a Boolean function of the states of the nodes that regulate it
- Choose between synchronous/asynchronous update
- Start with a known or assumed initial condition.
- The state of the whole network changes in time. Identify the attracting (long-term) state or behavior of the system.
- Consider other relevant initial conditions. Map the relationship between initial and attracting states.

Ex. 5

Construct a network of three nodes, such that their in-degree is one or two. Associate a Boolean rule to each node. Assume that each node's state changes at the same time (synchronous update).

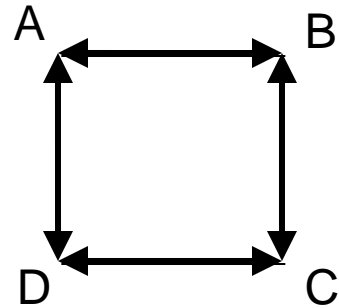
Start with an initial state, and update the state of the nodes 10 times.

What is happening to the state of the network?

Start from a different initial state. Is the final behavior be the same?

How many different final states/behaviors can the network have?

## Example

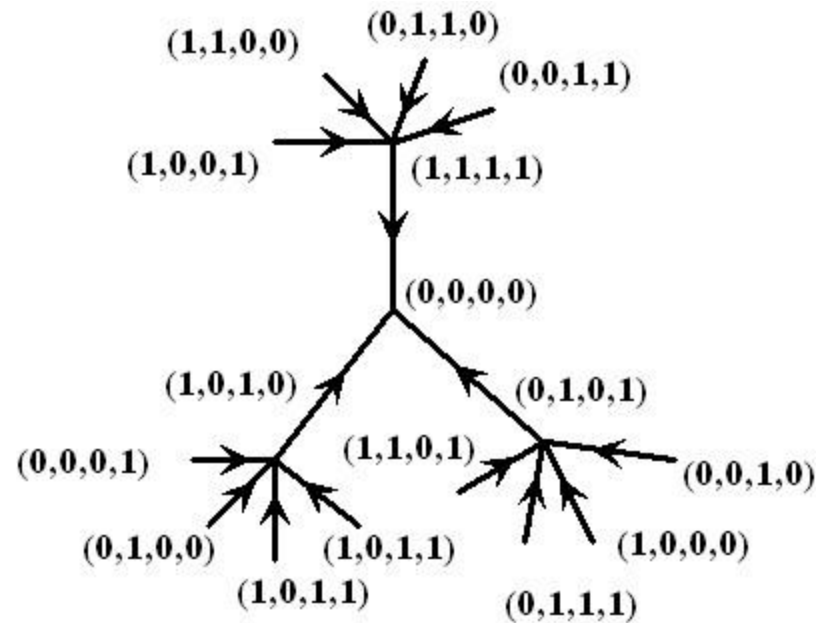


I1	I2	O
0	0	0
0	1	1
1	0	1
1	1	0

## States

A	B	C	D
0	0	0	0
0	0	0	1
....	...	...	...
1	1	1	1

## Transitions



# Concepts in Boolean network dynamics

**Attractor** – a set of states that repeats itself, can be a **fixed point** or a **complex attractor**

Fixed point: Future State = Current State = Previous State

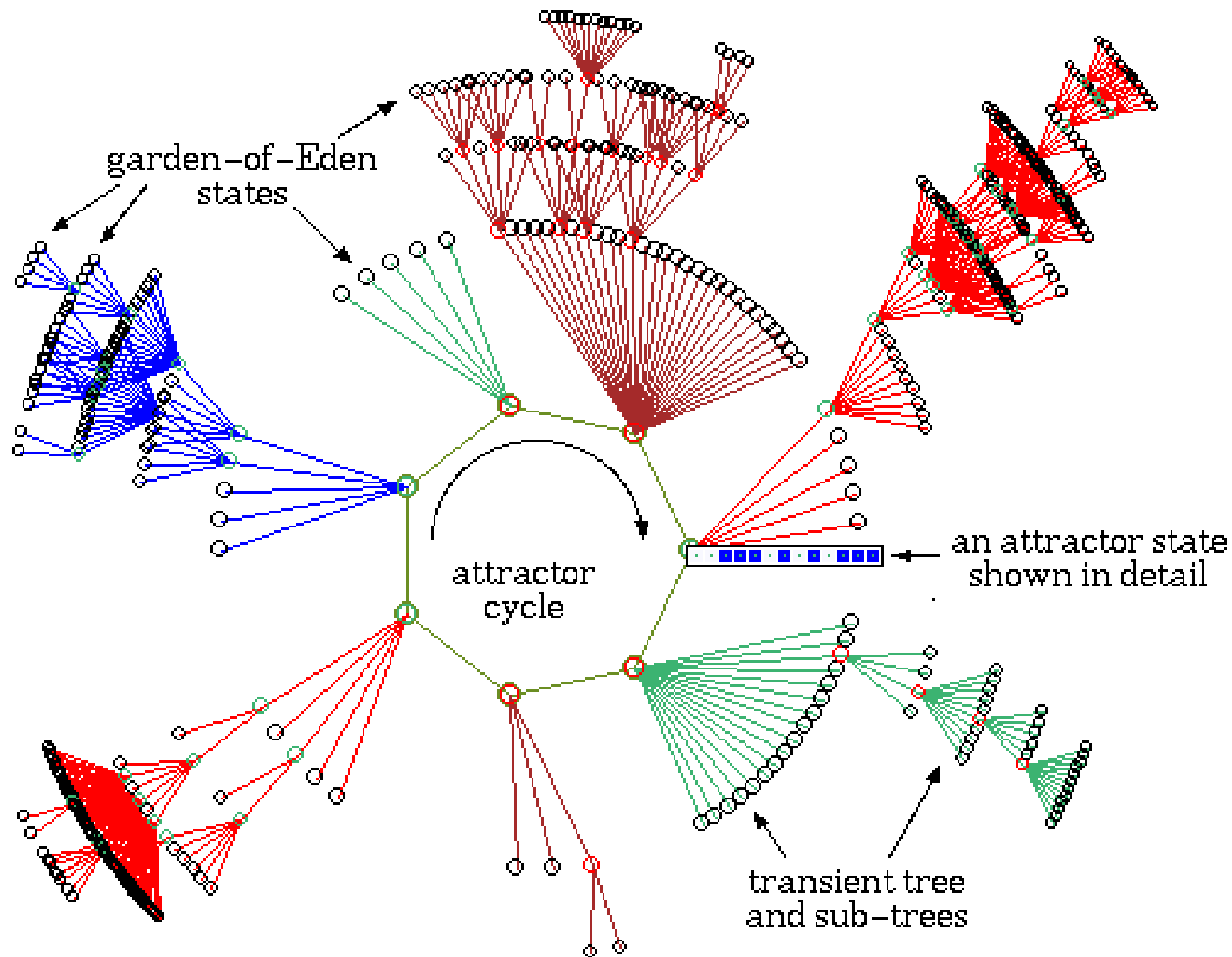
All states lead to or are part of an attractor.

**Basin of attraction** – all states leading to a given attractor

In a network of  $N$  nodes the maximum possible size of an attractor is the total number of states,  $2^N$

In practice, the size of the attractor is much shorter than this maximum.

# State transition graph for a synchronous Boolean model





In practice, the size of attractors is much shorter than the maximum.

Cause: many nodes become **frozen**, due partly to **canalizing functions**.

**Canalizing** (forcing) functions:

At least one of the inputs has the property that the output is fixed if this input has one particular value.

e.g.  $a \text{ AND } b$  is canalizing because  $a=0$  implies  $a \text{ AND } b = 0$

Ex. 6

How many two-input Boolean functions are there?

How many of them are canalizing?

Ex. 7. Consider a network of four nodes. Node A is the signal, the Boolean rules of the other three nodes are the following:

$$B^* = A \text{ or } C, \quad C^* = A \text{ and not } D, \quad D^* = B \text{ and } C$$

Set  $A = 0$ .

(a) Assume that each node's state changes at the same time (synchronous update). Start with an initial state, and update the state of the nodes 5 times.

What attractor did you find?

(b) Now start from the same initial state, but update only one, randomly selected, node at each step.

Is the result the same?

Q. How can you determine the fixed points of a Boolean model without performing updates?

In the fixed point time does not matter, thus the transfer functions become equations

$$A = 0$$

$$B = A \text{ or } C$$

$$C = A \text{ and not } D$$

$$D = B \text{ and } C$$

$$\text{Solution: } A = 0, B = 0, C = 0, D = 0$$

Asynchronous models have the same fixed points as synchronous ones.

Ex. 8

Consider the same network of four nodes.

$B^* = A \text{ or } C$ ,  $C^* = A \text{ and not } D$ ,  $D^* = B \text{ and } C$

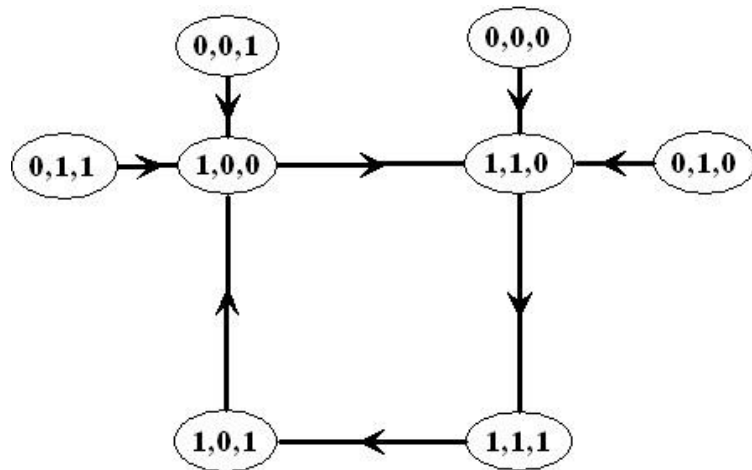
Set  $A = 1$ .

(a) Assume that each node's state changes at the same time (synchronous update). Start with an initial state, and update the state of the nodes 10 times.

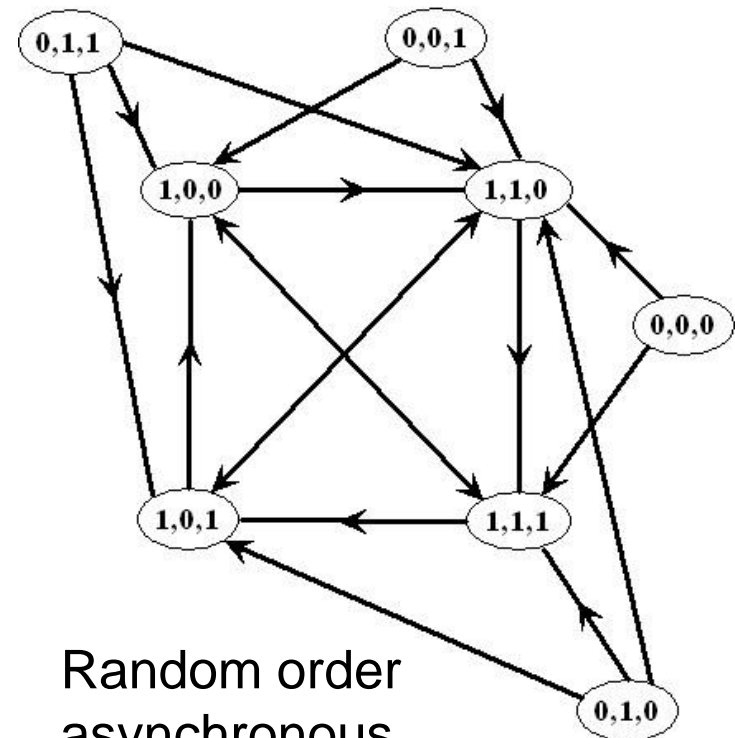
What attractor did you find? Is it the same as for  $A = 0$ ?

(b) Now start with the same initial state, but update the nodes in a randomly selected order at each step. What is the attractor now?

# Attractors for synchronous and asynchronous models



Synchronous

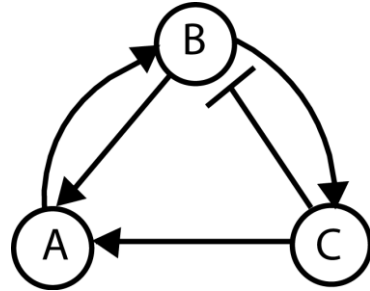


Random order  
asynchronous

The analog of a periodic orbit in a synchronous model is a strongly connected component with empty out-component in the state space of an asynchronous model.

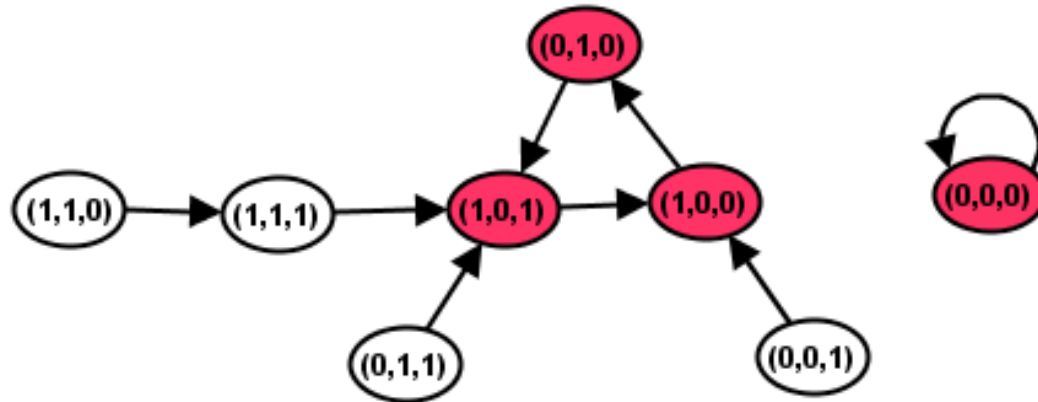
# Comparison of state transition graphs of synchronous and asynchronous models

Example



Node	Boolean rule
A	$A^* = B \text{ OR } C$
B	$B^* = A \text{ AND } (\text{NOT } C)$
C	$C^* = B$

Synchronous state transition graph:

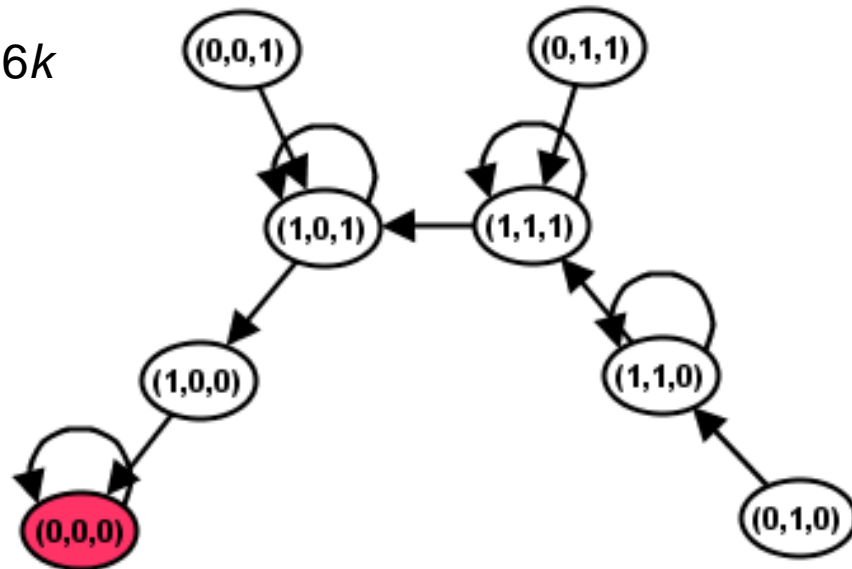


- Each state has one and only one possible successor
- There is a fixed point and an extended attractor (limit cycle) of size 3

# Deterministic asynchronous state transition graph

Each node has an associated time unit and is updated at multiples of its time unit

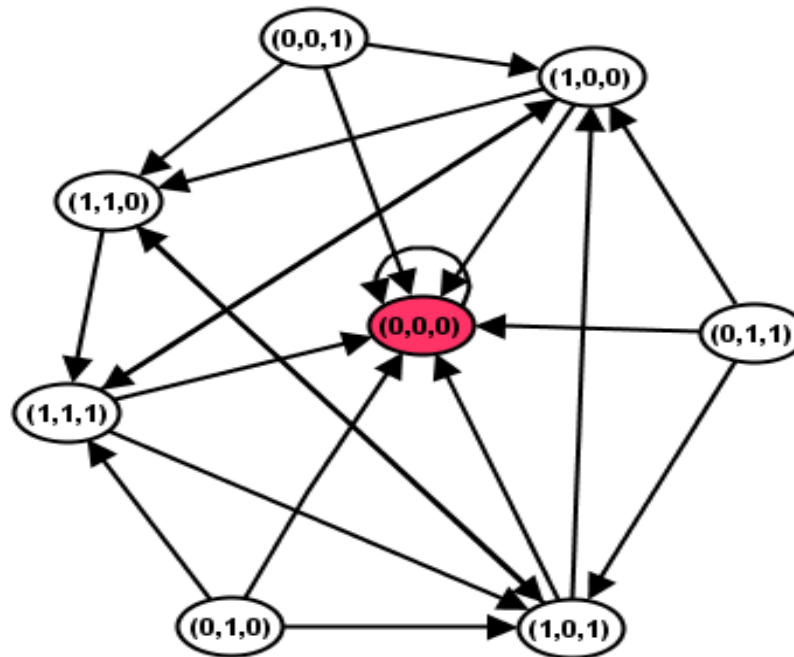
Given  $T_A = 2k$ ,  $T_B = 3k$  and  $T_C = 6k$



- Self loops appear when a node is updated but its state does not change
- For the given time units, only the fixed point of synchronous model is reached. There might exist some time units leading to complex attractors

# Random order asynchronous state transition graph

Select a random update order in each time step and update the nodes in that order

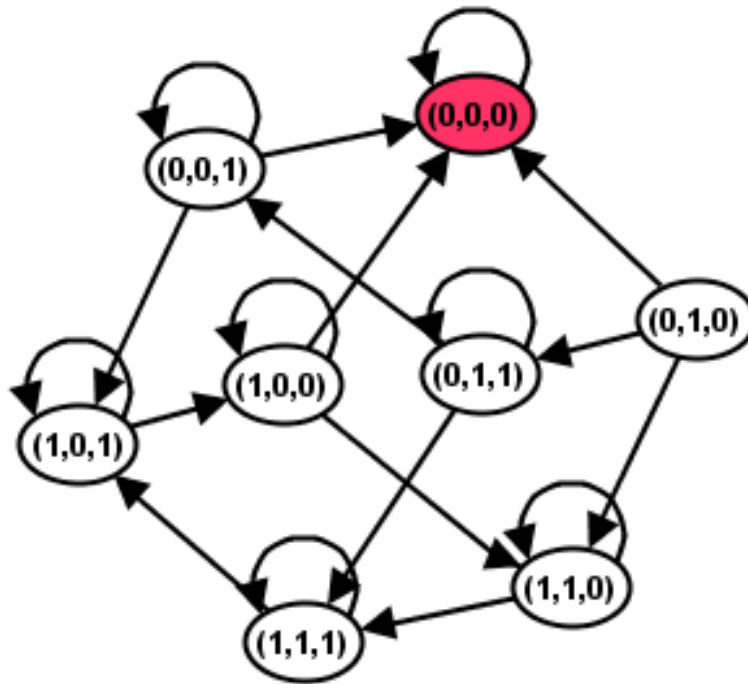


- Each state can have multiple successors
- In this particular example, only the fixed point of the synchronous model is reached



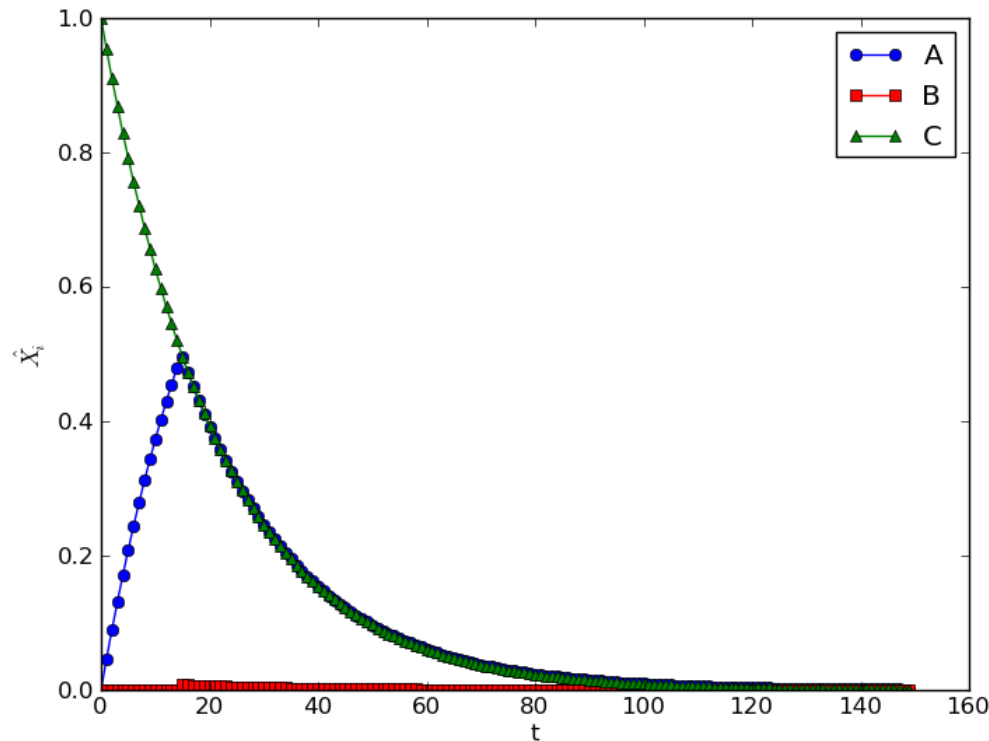
# General asynchronous state transition graph

Update a randomly selected node in each time step



- Each state can have multiple successors
- Self loops appear when a node is updated but its state does not change
- In this particular example, only the fixed point of synchronous model is reached

# Hybrid model for initial state $A=B=0$ and $C=1$



- The fixed points of the hybrid model are the same as those of the corresponding Boolean model

Synchronous, asynchronous and hybrid models can be implemented in BooleanNet <http://code.google.com/p/booleannet/>

# Boolean modeling of gene regulatory networks in the absence of data

Stuart Kauffman ~ 1965, NK model

Ideas:

- genes can be modeled by on-off switches
- the gene regulatory functions are unknown
- the structure of the gene regulatory networks is unknown
- the attractors of the gene reg. network correspond to cell types

- Construct a network where each node's in-degree is  $K$ .
- Assume that the state of each node can be 0 or 1.
- The state of each node is updated synchronously at each timestep.
- The rule giving the new state of each node is a randomly selected (and then fixed) Boolean function of the states of its regulators.
- Find the attractors of the network states.

How does the number and type of attractors change with  $N$  and  $K$  ?

# Attractors in Kauffman (NK) networks

- For  $K=1$ , networks are frozen  
median number of attractors is close to  $2^N$   
median cycle length close to 1
- For  $K>5$ , networks are chaotic  
few attractors  
median cycle length close to  $2^N$
- For  $K=2$ , interesting level of order  
median number and length of attractors both scale close to linearly  
with  $N$

This is fairly similar with the number of cell types in different organisms.

# Stability of Kauffman networks

What is the effect of a “mutation”, changing the state of a randomly selected node?

If the final number of changed nodes is small – frozen network

Cascading changes affect most of the network – chaotic network

The threshold between order and chaos in the NK model is  $K_c=2$ . This threshold is maintained if the underlying network is an Erdős – Rényi random graph with  $\langle k_{in} \rangle = K$ .

If the underlying network has a power-law degree distribution, the threshold between order and chaos is  $\gamma = 2.5$

The dynamics of scale-free networks with  $\gamma > 2.5$  are robust to random perturbations.

M. Aldana, P. Cluzel, PNAS 100, 8711 (2003)

As we find out more about gene regulatory networks, it is not necessary to assume random topologies and regulatory functions anymore.

It is still interesting to see how successful an ON/OFF framework and Boolean logic can be as compared to chemical kinetics-based models.

Example: Boolean modeling of the segment polarity gene network

Continuous: G. von Dassow et al., Nature 406, 188 (2000)

Synchronous Boolean: R. Albert, H. G. Othmer, Journ. Theor. Biol. 223, 1 (2003)

Asynchronous Boolean: M. Chaves, R. Albert, E. Sontag Journ. Theor. Bio. 235, 431 (2005).

Continuous- Boolean hybrid: M. Chaves, E. Sontag, R. Albert, IEE Proc. Systems Biology (2006).